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RESEARCH

# Comparison of clinical and safety outcomes in patients with *Stenotrophomonas maltophilia* bacteremia: a trimethoprim/sulfamethoxazole versus levofloxacin monotherapy

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## Abstract

**Purpose** The study aimed to compare the clinical outcomes and safety of trimethoprim/sulfamethoxazole (TMP/SMX) versus levofloxacin monotherapy in patients with monomicrobial *Stenotrophomonas maltophilia* (*S. maltophilia*) bacteremia.

**Methods** We conducted a retrospective cohort study of adult inpatients with *monomicrobial S. maltophilia* bacteremia at a tertiary medical center in Taiwan from January 2004 to June 2025. Patients were divided into two groups for comparison based on antibiotic treatment: TMP/SMX and levofloxacin monotherapy. Primary outcome was 30-day mortality. Secondary outcomes included in-hospital mortality, clinical response, microbiological eradication, non-susceptible strains emergence, recurrent bacteremia, and adverse drug reactions. Multivariable logistic regression and propensity score analysis were performed using inverse probability of treatment weighting (IPTW).

**Results** Among 226 patients, 129 received levofloxacin and 97 received TMP/SMX. The levofloxacin-treated group was associated with lower 30-day mortality (17.8% vs. 36.1%, $p=0.002$) in the primary analysis. In the multivariable logistic regression model, levofloxacin use was independently associated with improved outcomes ($p=0.047$). Similarly, in the IPTW analysis, levofloxacin use remained a factor of lower 30-day mortality ($p=0.026$). Additionally, microbiological eradication, emergence of non-susceptible strains, and recurrent bacteremia were comparable between the treatment groups, while adverse events were significantly less frequent in patients treated with levofloxacin (3.1% vs. 25.8%, $p<0.001$).

**Conclusions** Levofloxacin appeared to be more effective and safer than TMP/SMX in this retrospective analysis; however, this interpretation should be made with caution given the observational nature of the study. Further randomized clinical trials are warranted to validate these findings.

**Keywords** Stenotrophomonas maltophilia · Bacteremia · Bloodstream infections · Levofloxacin, trimethoprim/Sulfamethoxazole, levofloxacin

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## Introduction

*Stenotrophomonas maltophilia* (*S. maltophilia*), previously known as *Xanthomonas maltophilia* or *Pseudomonas maltophilia*, is a Gram-negative opportunistic bacterium that is widely distributed in aquatic environments and has become a significant nosocomial pathogen in recent years [1]. It primarily infects immunocompromised patients and can cause various types of infections, with pneumonia being the most common, followed by bacteremia [1, 2]. Mortality rates associated with *S. maltophilia* bacteremia vary considerably, ranging between 14 and 62%, with an attributable mortality rate of 26.7% [3, 4].

Treatment of *S. maltophilia* infections is challenging due to its intrinsic and acquired multidrug resistant mechanisms, which limit therapeutic options [5]. The 2024 IDSA guidelines recommend combination therapy with at least two in vitro active agents for all Stenotrophomonas maltophilia infections, based primarily on in vitro data [6]. Nevertheless, clinical evidence has not demonstrated superior efficacy of combination therapy compared with monotherapy for *S. maltophilia* infections, and concerns remain regarding the increased cost and risk of adverse reactions associated with combination treatment. Accordingly, the consensus document of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) recommends combination therapy only for severe *S. maltophilia* infections in immunocompromised patients. In other clinical settings, monotherapy with either trimethoprim/sulfamethoxazole (TMP/SMX) or levofloxacin is advised [7]. In terms of monotherapy, TMP/SMX has been considered the mainstay treatment due to its in vitro activity against most *S. maltophilia* isolates and favorable outcome reports [8, 9]. In cases of TMP/SMX resistance or when its administration is contraindicated due to a life-threatening allergy, fluoroquinolones, primarily levofloxacin, have been the most commonly used alternative agents according to the literature reviewed [10]. Two systematic reviews and meta-analyses have reported the efficacy comparison of fluoroquinolones versus TMP/SMX in the treatment of *S. maltophilia* infections [11, 12]. From both studies, the results demonstrated lower mortality associated with fluoroquinolone use compared with TMP/SMX; however, the superior efficacy of fluoroquinolone was not observed in subgroup analyses focusing on bacteremia, possibly due to the small sample size analyzed. Besides the efficacy comparison between fluoroquinolones and TMP/SMX, safety outcomes have been less frequently discussed in the literature. Although different fluoroquinolones have been used for *S. maltophilia* infections, only levofloxacin has the established breakpoint according to the Clinical & Laboratory Standards Institute (CLSI) and is suggested by recent Infectious Diseases Society of America (IDSA) guidance for *S. maltophilia* infection [6]. Therefore, levofloxacin is a better representative of fluoroquinolones to compared clinical efficacy with TMP/SMX in the treatment of *S. maltophilia* infection. This study aimed to compare the clinical and safety outcomes of patients with *S. maltophilia* bacteremia receiving levofloxacin monotherapy to those treated with TMP/SMX monotherapy.

## Methods

### Study design and participants

This retrospective cohort study was conducted at the Tri-service General Hospital (TSGH) located in Taiwan. Hospitalized adult patients (age > 18 years) with *S. maltophilia* bacteremia between January 1, 2004 and June 30, 2025 identified from the TSGH microbiological laboratory database were included. Each patient was included only once using first positive blood culture result within the admission. Patients with *S. maltophilia* bacteremia were included in the study if they received either TMP/SMX or levofloxacin monotherapy directed at *S. maltophilia* for > 48 h and if the causative *S. maltophilia* isolate was susceptible to the antibiotic prescribed. Patients were excluded if they had polymicrobial bacteremia, TMP/SMX or levofloxacin non-susceptible *S. maltophilia* bacteremia, received treatment with antibiotics other than TMP/SMX or levofloxacin for *S. maltophilia* bacteremia, died within 48 h of TMP/SMX or levofloxacin treatment, combination of other antibiotics with in vitro activity against *S. maltophilia* besides TMP/SMX or levofloxacin, sequential treatment with TMP/SMX and levofloxacin in either order. The included patients were classified into two groups: TMP/SMX and levofloxacin groups for comparison. Primary outcome of the study was overall 30-day mortality. Secondary outcomes included overall in-hospital mortality, clinical response at end of treatment (EOT), microbiologic eradication, non-susceptible strains emergence, recurrence bacteremia after EOT, and adverse reactions related to TMP/SMX or levofloxacin use.

### Data collection and definitions

Clinical data of the included patients (demographic information, underlying diseases at admission, source of bacteremia, clinical condition at bacteremia onset, antibiotic treatment, clinical and microbiologic outcomes, and safety outcomes related to TMP/SMX or levofloxacin use) were extracted from electronic medical records.

Hospital-acquired infection was defined according to criteria previously reported [13]. Chronic renal insufficiency was defined as creatinine levels >3 mg/dL. The Charlson

Comorbidity Index score was employed as a composite measure to quantify the burden of underlying diseases [14]. Determination of bacteremia origin was based on the CDC/NHSN surveillance definitions for specific Types of Infections [15]. Disease severity on the day of bacteremia onset was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [16]. Septic shock was defined according to the Third International Consensus Definition for septic shock [17]. Acute kidney injury of stage 2 or 3 severity was recorded according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [18]. Co-infections were defined as other bacterial infections occurring within 48 h of *S. maltophilia* bacteremia. Bacterial co-infections were classified using CDC surveillance criteria and confirmed by culture results [15]. Two senior infectious disease specialists (F.-Y.C., and J.-C.L.) reviewed all co-infections to distinguish infection from colonization. The treatment dosages of TMP/SMX and levofloxacin were determined by the attending physicians in consultation with infectious disease specialists based on patients' clinical condition and renal function. Optimal treatment dosage was determined if patients with normal renal function received levofloxacin at 750 mg per day or 10–15 mg/kg of TMP/SMX per day (trimethoprim component) [6]. Levofloxacin dosages were adjusted for renal impairment according to the 2024 Sanford Guide. When the estimated creatinine clearance (eCrCl), calculated using the Cockcroft–Gault equation, was between 20 and 49 mL/min or < 20 mL/min, levofloxacin dosages were adjusted to 750 mg and 500 mg every 48 h, respectively [19]. For TMP/SMX, no adjustment was required when eCrCl ≥ 30 mL/min, while a 50% reduction was applied when eCrCl < 30 mL/min [20]. Combination therapy characterized by using additional antibiotics beyond TMP/SMX or levofloxacin directed to coinfections with other organisms were recorded. Immediate effective therapy of TMP/SMX and levofloxacin against *S. maltophilia* within 48 h of bacteremia onset was recorded. Documented source control measures included removal of preexisting central venous catheter or drainage of local abscess thought to be the source of bacteremia. The 30-day mortality was defined as death within 30 days of index culture and in-hospital mortality was defined as death due to any cause after bacteremia onset at any time within current admission. Clinical response at EOT was evaluated by two senior infectious disease specialists (F.-Y.C. and J.-C.L.) and defined as the improvement of all signs and symptoms related to infection accompanied together with normalization or improvement of inflammatory biomarkers, including C-reactive protein or procalcitonin levels. Microbiologic eradication was described as negative blood culture for *S. maltophilia* on repeated culture during or after the EOT. Patients who did not have a repeat culture were excluded. Non-susceptible *S. maltophilia* emergence was defined as subsequent.

*S. maltophilia* isolation from any sites within 30 days after treatment showing non-susceptibility against targeted antibiotic TMP/SMX or levofloxacin. Recurrence of bacteremia was defined as *S. maltophilia* occurrence within 30 days following documented eradication of the initial bacteremia. Patients were also evaluated for adverse drug reactions (ADRs) related to administrated drug by three investigators (W-P.C., J-L.C. and C.-H.W.) using the Naranjo Adverse Drug Reaction Probability Scale and the Hartwig Scale was used to categorize adverse drug reaction severity described in our previous study [21].

## Microbiology

Identification of *S. maltophilia* was conducted using the VITEK 2 automated system (bioMérieux, Marcy-l'Étoile, France) between 2004 and 2015. This was replaced with Matrix-assisted laser desorption/ionization–time of flight mass spectrometry (bioMerieux, Marcy l'Etoile, France) since 2016. Drug susceptibility test for levofloxacin and TMP/SMX in the identified *S. maltophilia* was conducted using the VITEK 2 system. Additionally, minocycline was tested for susceptibility using a disk diffusion method since 2022. The breakpoint interpretation for TMP/SMX (≤2/38 μg/mL, and >4/76 μg/mL, resistance) and levofloxacin (≤2 μg/mL, susceptibility; 4.0 μg/mL, intermediate; and ≥8 μg/mL, resistance) was in accordance with the 2024 CLSI. Carbapenem-resistant (CR) organisms from co-cultured bacteria with *S. maltophilia* were defined as resistant to at least one carbapenem.

## Statistical analysis

A software package (SPSS, version 27.0; SPSS Inc., Chicago, IL, USA) was used to analyzed all data in the current study. A comparison was performed for patients who received TMP/SMX and those who received levofloxacin, as well as for survivors versus non-survivors at 30-day after bacteremia. Continuous variables were described as median and interquartile ranges; number and percentages were used to report categorical variables. Normality distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. The Mann–Whitney U or Student's t tests were used to compare continuous variables as appropriate. The Chi–Square or Fisher's exact test was used to compared categorical variables between the groups. A $p$-value of < 0.05 was used to consider statistically significant differences. A multivariable logistic regression model was performed to ascertain risk factors independently associated with all cause in hospital-mortality. Variables in the

model were included for the final multivariable model if they had a $p$-value of < 0.1 from the univariable analysis between the survivors and non survivors. To address non-randomized treatment assignment of antibiotics, we developed a multivariable logistic regression model to estimate propensity score (PS) of each patient receiving levofloxacin. Covariates included to generate the PS were identified by selecting variables with $p$-values < 0.1, both in the comparison between levofloxacin and TMP/SMX treated patients and survivors versus non-survivors. Weighting PS using inverse probability of treatment weighting (IPTW) was then performed to assess the causal effect (precisely, the average treatment effect) of levofloxacin compared with TMP/SMX, with an assumption of selection of observables [22]. A patient who received levofloxacin was weighted using the inverse probability of treatment that he or she would be treated with levofloxacin, and a patient who received TMP/SMX was weighted using the inverse probability that he or she would be treated with TMP/SMX, equivalent to 1 minus his or her PS. Balance of the propensity model was evaluated by verifying the obtained balance of PS covariates and comparing the baseline characteristics of the two treatment groups after applying the IPTW [23]. After that, propensity-weighted multiple logistic regression models were performed to ascertain risk factors independently associated with in-hospital mortality.

### Sensitivity analysis

We conducted a sensitivity analysis excluding patients who received combination antibiotic therapy with potential activity against *S. maltophilia*—including tigecycline, quinolones, colistin, and ceftazidime—to minimize confounding effects of these agents. After exclusion, we reassessed the association between levofloxacin and TMP/SMX use and mortality using both univariable and multivariable logistic regression analyses, thereby evaluating the impact of concomitant active antibiotics as potential confounders.

## Results

### Study population

A total of 755 patients were identified at first *S. maltophilia* bacteremia during the study period. After exclusion, 226 patients were included in the study for further investigation: 129 received levofloxacin and 97 patients were treated with TMP/SMX. The flow chart of case selection is represented in Fig. 1.

Baseline characteristics of the two treatment groups are summarized in Table 1. Of 226 patients included in the study, 152 (67.3%) were males, and median age was 71.5 years. Most of the included patients had hospital acquired infection (209/226, 92.5%). The median Charlson Comorbidity Index score of all included patients was three. Patients receiving levofloxacin were younger and had lower Charlson Comorbidity Index scores than those receiving TMP/SMX ($p=0.043$ and 0.018, respectively). Regarding the sources of bacteremia, respiratory tract infections were the most common (104/226, 46.0%). A numerically higher proportion of CLABSI (central line–associated bloodstream infection) cases was observed in the levofloxacin group (34.1% vs. 22.7%), but the overall distribution of bacteremia sources did not differ significantly between the two groups ($p=0.151$). At the onset of bacteremia, the overall median APACHE II score was 19. The levofloxacin group had lower median APACHE II scores than the TMP/SMX group (18 vs. 21, $p=0.008$), and there was no statistically significant difference between groups in terms of septic shock, co-infections with other bacteria including CR-organisms (All $p>0.05$). Different Co-infections with causative cultured pathogens and CR-organisms were shown in Supplementary Tables 1 to 3#.

Regarding bacteremia treatment, source control measures were more frequently performed in patients receiving levofloxacin with borderline significance (24.8% vs. 15.5%, $p=0.087$). A higher proportion of patients in the levofloxacin group received immediate therapy compared with the TMP/SMX group (20.2% vs. 9.3%, $p=0.025$). The median daily dose was 750 mg for levofloxacin and 5.6 mg/kg (TMP component) for TMP/SMX. Optimal dosing was less frequent in the TMP/SMX group than in the levofloxacin group (33.3% vs. 62.0%, $p<0.001$). Among TMP/SMX patients without optimal dosing ($n=65$), most (55/65, 84.6%) received suboptimal doses. Combined antibiotics for coinfections were shown in Supplementary Table 4. Carbapenems were the most common additional antibiotic (66/226, 29.2%).

### Primary outcome

As shown in Table 2, the overall 30-day mortality rate of patients with *S. maltophilia* was 25.7%. Patients in the levofloxacin group exhibited significantly lower 30-day mortality (17.8% vs. 36.1%, $p=0.002$) than those in the TMP/SMX group. The Kaplan–Meier survival curve showed a consistent result, suggesting that levofloxacin is associated with better survival outcomes (Log-rank test $p=0.002$, Fig. 2). A comparison of patients who died or not at 30-day after bacteremia is presented in Table 3. Several variables between the groups with $p$ values of <0.1 were found including chronic obstructive pulmonary disease, focus of bacteremia, APACHE II score, septic shock, levofloxacin use, and

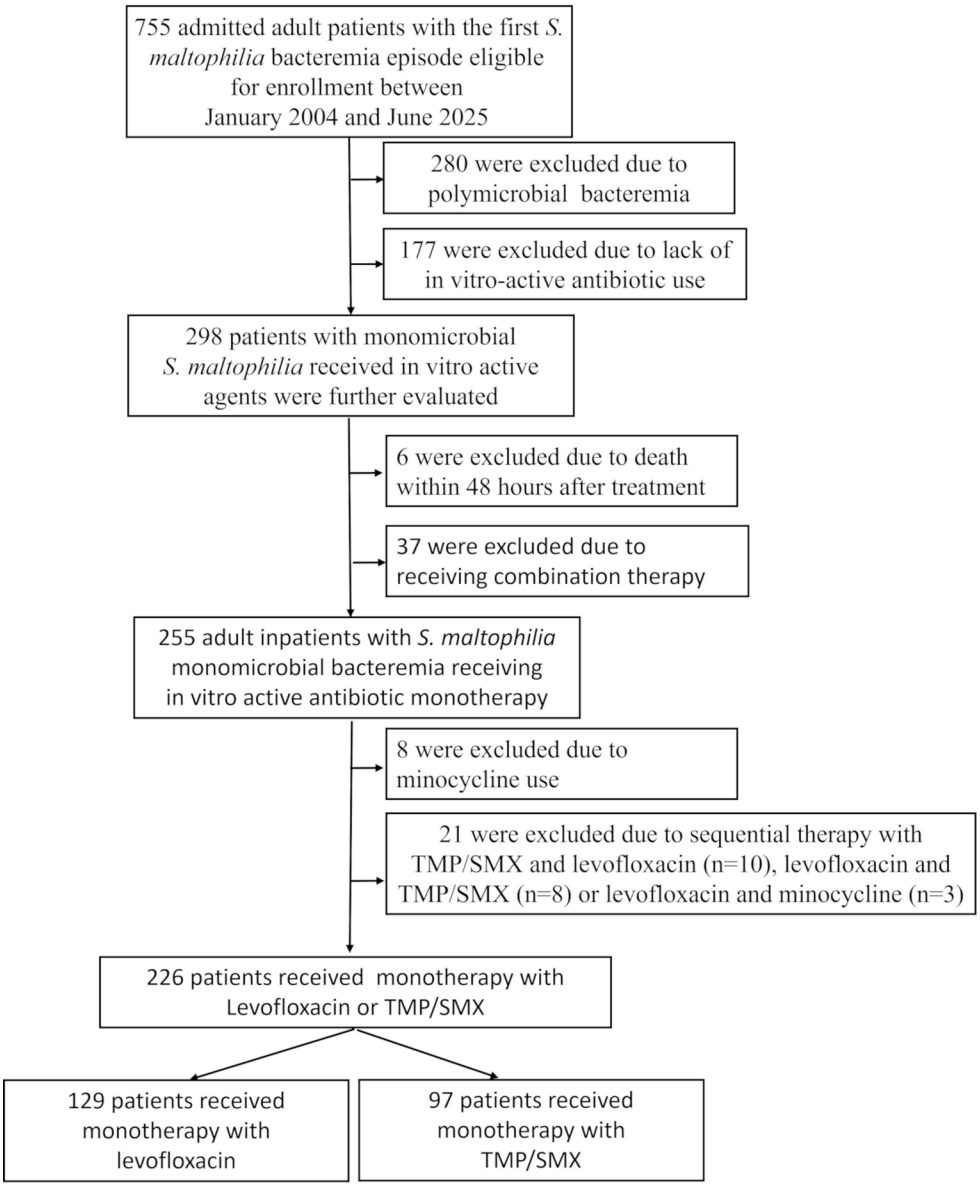
755 admitted adult patients with the first S. maltophilia bacteremia episode eligible for enrollment between January 2004 and June 2025
280 were excluded due to polymicrobial bacteremia
177 were excluded due to lack of in vitro-active antibiotic use
298 patients with monomicrobial S. maltophilia received in vitro active agents were further evaluated
6 were excluded due to death within 48 hours after treatment
37 were excluded due to receiving combination therapy
255 adult inpatients with S. maltophilia monomicrobial bacteremia receiving in vitro active antibiotic monotherapy
8 were excluded due to minocycline use
21 were excluded due to sequential therapy with TMP/SMX and levofloxacin (n=10), levofloxacin and TMP/SMX (n=8) or levofloxacin and minocycline (n=3)
226 patients received monotherapy with Levofloxacin or TMP/SMX
129 patients received monotherapy with levofloxacin
97 patients received monotherapy with TMP/SMX

**Fig. 1** Flow chart of case selection

source control measure. Variables with $p<0.1$ at univariable analysis both in the comparison between different treatment regimens, and survivors versus non-survivors were then entered into the multivariable regression analysis (Table 4), APACHE II score (adjusted odds ratio [aOR] = 1.10, 95% confidence interval [CI] = 1.04–1.17, $p<0.001$) and septic shock (aOR = 2.31, 95% CI = 1.06–5.04, $p=0.035$) were independently associated with 30-day mortality, while levofloxacin use (aOR = 0.48, 95% CI = 0.23–0.98, $p=0.047$) was a protective factor for mortality after adjustment.

A PS of receiving levofloxacin was calculated. Variables with $p$-values < 0.1 for both the treatment and outcome groups (Tables 1 and 3) included in the PS were age, Charlson Comorbidity Index score, APACHE II score, source control measure, optimal treatment dosage of levofloxacin or TMP/SMX, chronic obstructive pulmonary disease, levofloxacin or TMP/SMX use in 48 h after bacteremia, respiratory tract infection, and septic shock. The balance of baseline comparison and PS covariates after applying the IPTW of the two treatment groups were reported in Supplementary Table 7. The included covariates were all balanced after PS estimation with standardized mean difference < 0.10 except for APACHE II score. In the IPTW-adjusted multivariable regression analysis (Table 4), levofloxacin use was still associated with lower 30-day mortality compared with TMP/SMX (aOR = 0.45, 95% CI = 0.22–0.90, $p=0.026$).

**Table 1** Clinical characteristics of patients with *S. maltophilia* bacteremia receiving Levofloxacin versus TMP/SMX

| Characteristic[a] | Total ($n=226$) | Levofloxacin ($n=129$) | TMP/SMX ($n=97$) | $p$–value |
|---|---|---|---|---|
| Age, years[b] | 71.5 (59–81) | 70 (56.0–79.0) | 74 (59.5–84.5) | 0.043 |
| Age > 65 | 141 (62.4) | 77 (59.7) | 64 (66.0) | 0.334 |
| Male sex | 152 (67.3) | 84 (65.1) | 68 (70.1) | 0.429 |
| Hospital acquired | 209 (92.5) | 121 (93.8) | 88 (90.7) | 0.385 |
| **Baseline underlying diseases** | | | | |
| Heart failure | 47 (20.8) | 28 (20.9) | 20 (20.6) | 0.954 |
| Dementia | 15 (6.6) | 8 (6.2) | 7 (7.2) | 0.762 |
| Chronic obstructive pulmonary disease | 17 (7.5) | 7 (5.4) | 10 (10.3) | 0.168 |
| Peptic ulcer disease | 51 (22.6) | 25 (19.4) | 26 (26.8) | 0.186 |
| Diabetes mellitus | 77 (34.1) | 42 (32.6) | 35 (36.1) | 0.580 |
| Cirrhosis of liver | 19 (8.4) | 11 (8.5) | 8 (8.2) | 0.940 |
| Chronic renal insufficiency | 48 (21.2) | 28 (21.7) | 20 (20.6) | 0.843 |
| Malignancy | 71 (31.4) | 39 (30.2) | 32 (33.0) | 0.659 |
| Autoimmune disease | 11 (4.9) | 6 (4.7) | 5 (5.2) | 0.862 |
| Charlson Comorbidity score[b] | 3 (2–5) | 3 (1–5) | 3 (2–6) | 0.018 |
| **Focus of bacteremia** | | | | 0.151 |
| Respiratory tract infection | 104 (46.0) | 58 (45.0) | 46 (47.4) | |
| CLABSI | 66 (29.2) | 44 (34.1) | 22 (22.7) | |
| Primary bacteremia | 47 (20.8) | 24 (18.6) | 23 (23.7) | |
| Others[c] | 9 (3.9) | 3 (2.3) | 6 (6.1) | |
| **Clinical condition at bacteremia onset** | | | | |
| APACHE II score[b] | 19 (14–24) | 18 (13–22) | 21 (15–26) | 0.008 |
| Septic Shock | 51 (22.6) | 28 (21.7) | 23 (23.7) | 0.721 |
| Co-infections with bacteria other than *S. maltophilia* | 84 (37.2) | 49 (38.0) | 35 (36.1) | 0.770 |
| Co-infections with CR-organisms | 50 (22.1) | 32 (24.8) | 18 (18.6) | 0.263 |
| **Source control measure** | 47 (20.8) | 32 (24.8) | 15 (15.5) | 0.087 |
| **Antibiotic treatment** | | | | |
| Effective Levofloxacin or TMP/SMX use in 48 h after bacteremia | 35 (15.5) | 26 (20.2) | 9 (9.3) | 0.025 |
| Optimal treatment dosage of Levofloxacin or TMP/SMX | 112 (49.6) | 80 (62.0) | 32 (33.0) | < 0.001 |

TMP/SMX, trimethoprim/sulfamethoxazole; CLABSI, central line–associated bloodstream infection; APACHE, Acute Physiology and Chronic Health Evaluation. CR, carbapenem resistant

[a]Data are presented as the number (percentage) of patients unless indicated otherwise

[b]Data are presented as median (interquartile range)

[c]One patient was due to skin or soft tissue infection; three were due to intra-abdominal infection, and the other five were due to urinary tract infection

## Secondary outcomes

The difference in mortality rates persists when in-hospital mortality was considered that patients who received levofloxacin were associated with lower mortality as shown in Table 2. In addition, patients who received levofloxacin were more likely to achieve clinical response at EOT than those received TMP/SMX (81.4% vs. 59.8%, $p<0.001$). With regards to microbiologic outcomes, no significant differences between the treatment groups in terms of microbiological eradication, recurrence of bacteremia, and non-susceptible strains isolation (All $p>0.05$). The overall microbiological eradication rate was high (92.6%) with no difference between levofloxacin and TMP/SMX groups (92.2% vs. 93.2%, $p=0.799$). Recurrent bacteremia occurred in 19/189 patients with eradication at EOT from patients with initial respiratory tract infections ($n=13$) and CLABSI ($n=6$). Most *S. maltophilia* isolates from recurrent bacteremia episodes showed unchanged antibiotic susceptibility compared with the initial episode, except for one isolate that developed resistance to both levofloxacin and TMP/SMX (Supplementary Table 5). Among patients with recurrent *S. maltophilia* bacteremia, seven received TMP/SMX, eleven received levofloxacin, and one received combination therapy with tigecycline and colistin for levofloxacin- and TMP/SMX-resistant *S. maltophilia* bacteremia. The

**Table 2** Treatment clinical outcomes among patients with *S. maltophilia* bacteremia receiving Levofloxacin versus TMP/SMX

| Characteristic[a] | Total | Levofloxacin | TMP/SMX | *p*–value |
|---|---|---|---|---|
| 30-day mortality | 58/226 (25.7) | 23/129 (17.8) | 35/97 (36.1) | 0.002 |
| Respiratory tract infection | 36/104 (34.6) | 14/58 (24.1) | 22/46 (47.8) | |
| CLABSI | 13/66 (19.7) | 6/44 (13/6) | 7/22 (31.8) | |
| Primary bacteremia | 6/47 (12.8) | 1/24 (4.2) | 5/23 (21.7) | |
| Others[b] | 3/9 (33.3) | 2/3 (66.7) | 1/6 (16.7) | |
| In-hospital mortality | 81/226 (35.8) | 34/129 (26.4) | 47/97 (48.5) | < 0.001 |
| Respiratory tract infection | 49/104 (47.1) | 20/58 (34.5) | 29/46 (63.0) | |
| CLABSI | 20/66 (30.3) | 11/44 (25.0) | 9/22 (40.9) | |
| Primary bacteremia | 7/47 (14.9) | 1/24 (4.2) | 6/23 (26.1) | |
| Others[b] | 5/9 (44.6) | 2/3 (66.7) | 3/6 (50.0) | |
| Clinical response | 163/226 (72.1) | 105/129 (81.4) | 58/97 (59.8) | < 0.001 |
| Respiratory tract infection | 65/104 (62.5) | 44/58 (75.9) | 21/46 (45.7) | |
| CLABSI | 42/47 (89.4) | 23/24 (95.8) | 19/23 (82.6) | |
| Primary bacteremia | 52/66 (78.8) | 37/44 (84.1) | 15/22 (68.2) | |
| Others[b] | 4/9 (44.4) | 1/3 (33.3) | 3/6 (50.0) | |
| Microbiological eradication[c] | 189/204 (92.6) | 107/116 (92.2) | 82/88 (93.2) | 0.799 |
| Respiratory tract infection | 91/100 (91) | 51/55 (92.7) | 40/45 (88.9) | |
| CLABSI | 57/60 (95.0) | 37/40 (92.5) | 20/20 (100) | |
| Primary bacteremia | 34/36 (94.4) | 17/19 (89.4) | 17/17 (100) | |
| Others[d] | 7/8 (87.5) | 2/2 (100.0) | 5/6 (83.3) | |
| Recurrence of bacteremia[e] | 19/189 (10.0) | 14/107 (13.0) | 5/82 (6.0) | 0.113 |
| Respiratory tract infection | 13/91 (14.2) | 9/51 (17.6) | 4/40 (10) | |
| CLABSI | 6/57 (10.5) | 5/37 (13.5) | 1/20 (5.0) | |
| Primary bacteremia | 0/34 (0) | 0/17 (0) | 0/17 (0) | |
| Others[f] | 0/7 | 0/2 (0) | 0/5 (0) | |
| Non susceptible strains isolation[g] | 32/224 (14.3) | 21/127 (16.5) | 11/97 (11.3) | 0.271 |
| Adverse drug reactions | 29 (12.8) | 4 (3.1) | 25 (25.8) | < 0.001 |

TMP/SMX, trimethoprim/sulfamethoxazole; CLABSI, central line–associated bloodstream infection

[a]Data are shown in number/total (percent)

[b]One patients were due to skin/soft tissue infection; three were due to intra-abdominal infection, and the other five were due to urinary tract infection

[c]Two hundred four cases had follow-up blood culture after bacteremia

[d]One patients were due to skin/soft tissue infection; two were due to intra-abdominal infection, and the other five were due to urinary tract infection

[e]One hundred eight-nine cases reached microbiological eradication after treatment were included

[f]Two were due to intra-abdominal infection, and the other five were due to urinary tract infection

[g]Two hundred twenty two cases had follow-up culture during or after treatment

30-day mortality rate among these patients was 31%. Subsequent isolation of non-susceptible strains was more frequent in the levofloxacin group, but not significant (16.5% vs. 11.3%, $p=0.271$; Table 2 and Supplementary Table 6). Adverse events were less frequent in patients with levofloxacin (3.1% vs. 25.8%, $p<0.001$, Table 5). Most events were moderate ($n=25$) while others were mild ($n=4$) severity per the Hartwig Severity Assessment Scale. In the TMP/SMX group, hyperkalemia was most common ($n=21$), leading to discontinuation in 5 patients (20%). In the levofloxacin group, 4 patients developed hepatitis and none discontinued therapy.

## Sensitivity analysis

A total of 57 included patients receiving combined antibiotics with ceftazidime, quinolones, colistin and tigecycline were excluded. After exclusion, patients in the levofloxacin group ($n=105$) still demonstrated a lower 30-day mortality rate (18.1% vs. 37.1%, $p=0.010$) compared with those in the TMP/SMX group ($n=64$). The data of logistic regression analysis were consistent with the primary analysis (Supplementary Table 8).

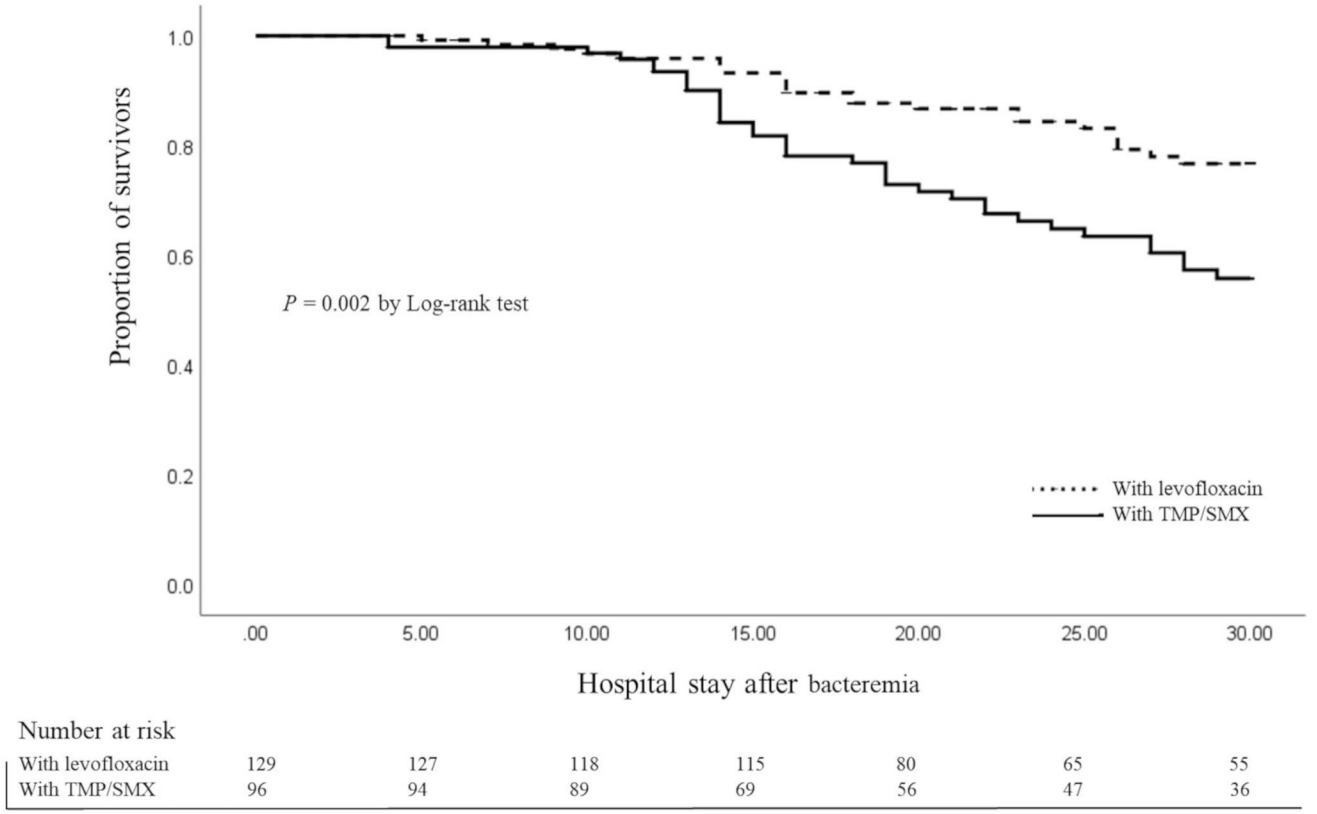


**Fig. 2** Kaplan–Meier survival curves for patients with *S. maltophilia* bacteremia receiving TMP/SMX or levofloxacin therapy

## Discussion

Clinical evidence comparing the outcomes of TMP/SMX and levofloxacin for *S. maltophilia* infections primarily comes from several observational studies, as randomized controlled trials are lacking [24–32]. In addition to the inherent limitations of retrospective studies, several critical factors in the reported studies may also affect the interpretation of the results. First, the relatively small sample size in the fluoroquinolone group may limit statistical power [24, 27, 29, 32]. Second, the inclusion of other fluoroquinolone classes without established breakpoints, in addition to levofloxacin, may introduce bias in the final outcome analysis [26, 27, 32]. Third, more virulent pathogens in polymicrobial infections, aside from *S. maltophilia*, may influence the outcomes and affect the interpretation of the results [24–26, 28, 30, 31]. Finally, distinguishing between colonization and true infection is challenging when *S. maltophilia* insolates cultured from non-sterile site [25, 26, 28–32]. Therefore, the current study focused on comparing patients with *S. maltophilia* monomicrobial bacteremia treated with TMP/SMX versus levofloxacin monotherapy to reduce the confounding factors observed in previous studies. Additionally, IPTW using PSs was employed to enhance the robustness and validity of our results. Our main finding is that levofloxacin use in patients is associated with lower 30-day and in-hospital mortality with better safety outcomes compared to TMP/SMX. The risk of subsequent emergence of non-susceptible strains, a concern in previous studies, is similar to that observed in patients receiving TMP/SMX [29].

Upon further assessment of the current study, several imbalanced variables were observed between the treatment groups. Patients receiving levofloxacin had lower Charlson Comorbidity Index and APACHE II scores, indicating that traditional TMP/SMX therapy was more often prescribed for critically ill patients with multiple comorbidities, possibly influenced by prior favorable outcome data [8]. Levofloxacin recipients were also more likely to undergo source control and receive immediate, optimally dosed therapy. These variables have been reported to affect outcome analysis in patients with bacteremia. We used multivariable logistic regression and the IPTW method to adjust for unbalanced variables, and levofloxacin remained associated with better survival. Three studies comparing fluoroquinolones with TMP/SMX in *S. maltophilia* bacteremia treatment showed a similar trend, though the results were not significant, likely due to their small sample sizes [24, 27, 33]. Subgroup analysis indicated that the overall superior efficacy of levofloxacin

**Table 3** Clinical characteristics of patients with *S. maltophilia* bacteremia who died or did not at 30-day after bacteremia

| Characteristic, *n* (%) | Survivors (*n* = 168) | Non-Survivors (*n* = 58) | *p*–value |
|---|---|---|---|
| Age, year[a] | 71 (58–80) | 73 (57.5–82.25) | 0.354 |
| Male sex | 114 (67.9) | 38 (65.5) | 0.743 |
| Hospital acquired | 154 (91.7) | 55 (94.8) | 0.570 |
| **Baseline underlying diseases** | | | |
| Heart failure | 32 (19.0) | 15 (25.9) | 0.270 |
| Dementia | 12 (7.1) | 3 (5.2) | 0.765 |
| Chronic obstructive pulmonary disease | 9 (5.4) | 8 (13.8) | 0.045 |
| Peptic ulcer disease | 36 (21.4) | 15 (25.9) | 0.486 |
| Diabetes mellitus | 55 (32.7) | 22 (37.9) | 0.472 |
| Cirrhosis of liver | 12 (7.1) | 7 (12.1) | 0.274 |
| Chronic renal insufficiency | 38 (22.6) | 10 (17.2) | 0.388 |
| Malignancy | 57 (33.9) | 14 (24.1) | 0.166 |
| Autoimmune disease | 7 (4.2) | 4 (6.9) | 0.479 |
| Charlson Comorbidity score[a] | 3 (2–5) | 3 (2–5) | 0.719 |
| **Focus of bacteremia** | | | 0.014 |
| Respiratory tract infection | 68 (40.5) | 36 (62.1) | |
| CLABSI | 53 (31.5) | 13 (22.4) | |
| Primary bacteremia | 41(24.4) | 6 (10.3) | |
| Others[b] | 6 (3.6) | 3 (33.3) | |
| **Clinical condition at bacteremia onset** | | | |
| APACHE II score[a] | 21(15–26) | 18(13–22) | 0.008 |
| Septic shock | 27 (16.1) | 24 (41.4) | < 0.001 |
| Co-infections with bacteria other than *S. maltophilia* | 66 (39.3) | 18 (31.0) | 0.262 |
| Co-infection with CR-organisms | 38 (22.6) | 12 (20.7) | 0.760 |
| **Antibiotic treatment** | | | |
| Levofloxacin use | 106 (63.1) | 23 (39.7) | 0.002 |
| Optimal treatment dosage of levofloxacin or TMP/SMX | 88 (52.4) | 24 (41.4) | 0.149 |
| Effective levofloxacin or TMP/SMX use in 48 h after bacteremia | 23 (13.7) | 12 (20.7) | 0.204 |
| **Source control measure** | 41 (24.4) | 6 (10.3) | 0.023 |

APACHE, Acute Physiology and Chronic Health Evaluation; CR, carbapenem resistant; TMP/SMX, trimethoprim/sulfamethoxazole; CLABSI, central line–associated bloodstream infection

[a]Data are presented as median (interquartile range)

[b]One patient was due to skin or soft tissue infection; three were due to intra-abdominal infection, and the other five were due to urinary tract infection

was primarily driven by its better outcomes in respiratory tract infections, which accounted for nearly half of the study population (104/226, 46.0%, Table 2). These findings are consistent with a recent multicenter study reporting better survival in *S. maltophilia* pneumoniae patients treated with levofloxacin compared with TMP/SMX [28]. Levofloxacin is known for its high epithelial lining fluid (ELF)-to-plasma concentration ratio, indicating excellent lung penetration [34]. No human data on the ELF-to-plasma ratio of TMP/SMX have been found. Only one in vivo study in horses reported that sulfadiazine (a related sulfonamide) and TMP had lower ELF-to-plasma ratios, suggesting suboptimal lung penetration compared with levofloxacin [35]. Therefore, the better clinical outcomes observed in bacteremia patients treated with levofloxacin may be attributable to its superior in vitro pharmacokinetic and pharmacodynamic properties compared with TMP/SMX. Regarding microbiologic outcomes, the overall microbiologic cure rate was 90.5% (90.2% for TMP/SMX and 90.7% for levofloxacin). Similar results have been reported, showing a 100% microbiologic cure rate for *S. maltophilia* bacteremia primarily treated with levofloxacin- or TMP/SMX -based regimens [25]. However, for studies involving *S. maltophilia* infections (mainly pneumonia) treated with levofloxacin or TMP/SMX, microbiologic cure rates were lower, ranging between 32 and 81.6% [26, 29, 30]. *S. maltophilia* tends to colonize the respiratory tract, particularly in immunocompromised patients with chronic respiratory diseases, those

**Table 4** Multivariable logistic regression and IPTW-adjusted analysis for factors associated with 30-day mortality

| Variable | Crude model | |
|---|---|---|
| | Adjusted OR (95% CI) | *p*–value |
| Multivariable logistic regression analysis[a] | | |
| Age | 0.99 (0.97–1.01) | 0.482 |
| Charlson Comorbidity score | 0.94 (0.80–1.09) | 0.445 |
| APACHE II score | 1.10 (1.04–1.17) | < 0.001 |
| Source control measure | 0.54 (0.17–1.74) | 0.307 |
| Optimal treatment dosage of levofloxacin or TMP/SMX | 0.52 (0.25–1.07) | 0.079 |
| Chronic obstructive pulmonary disease | 2.95 (0.88–9.88) | 0.079 |
| Effective levofloxacin or TMP/SMX use in 48 h after bacteremia | 1.64 (0.67–4.02) | 0.272 |
| Respiratory tract infection versus other infection sources | 1.33 (0.61–2.90) | 0.464 |
| Septic shock | 2.31 (1.06–5.04) | 0.035 |
| Levofloxacin versus TMP/SMX use | 0.48 (0.23–0.98) | 0.047 |
| IPTW-adjusted analysis | | |
| Levofloxacin versus TMP/SMX use | 0.45 (0.22–0.90) | 0.026 |

IPTW, inverse probability of treatment weighting; TMP/SMX, trimethoprim–sulfamethoxazole; APACHE, Acute Physiology and Chronic Health Evaluation; OR, odds ratio; CI, confidence interval

[a]Adjusted for age, Charlson Comorbidity score, APACHE II score, source control measure, optimal treatment dosage of levofloxacin or TMP/SMX, chronic obstructive pulmonary disease, effective levofloxacin or TMP/SMX use in 48 h after bacteremia, respiratory tract infection versus other infection sources, septic shock, and levofloxacin versus TMP/SMX use

**Table 5** Treatment safety outcomes among patients receiving Levofloxacin versus TMP/SMX

| Factors, *n* (%) | Total (*n* = 226) | Levofloxacin (*n* = 129) | TMP/SMX (*n* = 97) | *p*–value |
|---|---|---|---|---|
| Any adverse drug reaction | 29 (12.8) | 4 (3.1) | 25 (25.8) | < 0.001 |
| Skin rash | 2 | 0 | 2 | |
| Hyperkalemia[a] | 18 | 0 | 18 | |
| Agranulocytosis[b] | 2 | 0 | 2 | |
| Hepatitis[c] | 4 | 4 | 0 | |
| Hyperkalemia + acute kidney injury[d] | 2 | 0 | 2 | |
| Hyperkalemia + skin rash | 1 | 0 | 1 | |
| Discontinued antibiotic use due to adverse reactions[e], *n* = 29. | 5/29 (17.2) | 0/4(0) | 5/25 (20.0) | |

TMP/SMX, trimethoprim/sulfamethoxazole

[a]Blood serum potassium level > 5.5 mmol/L

[b]Blood absolute neutrophil count < 1500/μL

[c]Blood serum alanine aminotransferase and aspartate aminotransferase > 80 U/L

[d]Stage 2 and 3 severities according to Kidney Disease Improving Global Outcomes definition

[e]Data are shown in number/total patients with adverse drug reaction (percent)

with prior broad-spectrum antibiotic use, and individuals with prolonged hospital stays, all of which provide a selective advantage for its persistence [36, 37]. Consequently, respiratory infections by *S. maltophilia* are more difficult to reach microbiologic eradication than bloodstream infections, predisposing patients to subsequent recurrent invasive infections episodes. As shown in current study, most recurrent bacteremia cases (12/17, 70.6%) originated from the respiratory tract origin. Of note, the remaining recurrent cases were all linked to CLABSIs, underscoring the importance of source control in the management of *S. maltophilia* bacteremia. The selection of resistant strains is a critical consideration in antibiotic choice. *S. maltophilia* isolates can readily develop resistance to various classes of antibiotics, as demonstrated from in vitro studies [38]. Reported incidence of subsequent resistant *S. maltophilia* strain emergence to TMP/SMX and levofloxacin was between 3.7 and 20% and 3.6–30%, respectively, after treatment. No between group significant differences were observed [24, 26, 29, 32]. Our study yielded similar findings, with an overall isolation rate of non-susceptible strains of 14.7%. Notably, twelve of the 32 *S. maltophilia* isolates exhibited concurrent resistance to levofloxacin and TMP/SMX. The underlying resistance mechanism may be attributed to the overexpression of the efflux pumps SmeVWX or SmeDEF [39]. Nevertheless, the emergence of resistant strains in the present study appeared

unrelated to recurrent bacteremia, as most isolates from recurrent episodes remained susceptible to both antibiotics. (Supplementary Table 5). To improve treatment efficacy and reduce the emergence of resistance, the IDSA recommends combination therapy with at least two in vitro active agents for *S. maltophilia* infections, although relevant studies have shown inconsistent results [40]. Further studies are needed to validate the benefits of combination antibiotic therapy in *S. maltophilia* infections. Previous studies have shown that adverse events related to TMP/SMX use occur more frequently than with levofloxacin, with an incidence of up to 23.5% in TMP/SMX-treated patients [24, 27, 29]. In the current study, patients treated with TMP/SMX experienced more adverse events than those treated with levofloxacin (25.8% vs. 3.1%, $p < 0.001$), and hyperkalemia was most commonly reported adverse effect. TMP/SMX use is associated with several adverse effects, with hyperkalemia being particularly concerning due to its potential to cause life-threatening arrhythmias [41]. Previous studies have shown that hyperkalemia risk increases in patients receiving higher doses of TMP/SMX (TMP component 20 mg/kg/day) [2]. In our study, the median daily dose of TMP/SMX was only 5.6 mg/kg (TMP component), yet hyperkalemia was still observed in 21.6% of patients receiving TMP/SMX. These results may be explained by the fact that patients with *S. maltophilia* bacteremia often had multiple comorbidities and were receiving concurrent medications, which could alter TMP/SMX metabolism and increase the risk of hyperkalemia, despite dose adjustments based on renal function. Our results highlight the need for clinicians to be cautious of life-threatening complications when administering TMP/SMX, even if patients do not receive high-dose TMP/SMX.

This study has several limitations that warrant consideration. First, although PS weighting helped reduce selection bias, the imbalance between the two treatment groups due to unmeasured confounders remains a concern. These may include comorbid conditions not fully captured by the Charlson Comorbidity Index score, temporal variations in routine patient care over the study period, concurrent co-infections caused by non-bacterial pathogens (e.g., fungi or viruses), and other acute medical illnesses in addition to *S. maltophilia* bacteremia. Second, to maintain consistency across cases, most of the patients (approximately 50%) were excluded from our study. This exclusion may limit the generalizability of our findings to a broader clinical population. Third, patients with *S. maltophilia* infections often have concomitant bacterial co-infections, as previously reported [28, 30, 31]. In our study, 37.2% of included patients had bacterial co-infections. Consequently, these patients frequently received additional antibiotics (Supplementary Table 4). Although bacterial co-infections were documented in the current study and showed no significant difference on causative pathogens and infection types between treatment groups (Table 1; Supplementary Tables 1 to 3), the appropriateness of therapy for these co-infections was not controlled for, which may have influenced the final outcome analysis. Fourth, ADR cases were reassessed from documented records in the medical charts. Since all included patients typically had multiple concurrent medical conditions and were receiving various medications, these factors could have contributed to events resembling ADRs attributed to levofloxacin or TMP/SMX. Although the assessments were independently conducted by two senior infectious disease specialists using a standardized scoring system, the data may still be subject to bias. Finally, as a single-center study, our results may not fully apply to other real-world settings.

## Conclusions

Previous studies have suggested better efficacy of levofloxacin compared with TMP/SMX in treating overall *S. maltophilia* infections. Our study provides additional data showing superior clinical benefits (clinical response and mortality) of levofloxacin over TMP/SMX in patients with bacteremia. Besides, our data also revealed that patients received levofloxacin had better safety outcomes without increased resistance reemergence. Future randomized controlled trials are encouraged and urgently needed to establish the superior role of levofloxacin over TMP/SMX in treating *S. maltophilia* infections.

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**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Competing interests** The authors declare no competing interests.

**Ethics approval** This study was approved by the Institutional Review Board and Ethics Committee associated with Tri-Service General

Hospital of National Defense Medical Center (Approval No 2-101-05-074). The requirement for informed consent from each patient was waived because the study design was retrospective and anonymized patient and hospital data.

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